The Impact of Nicotine Dose on the Reinforcing Value of Cigarettes in Adolescents

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Objectives: The FDA is considering the implementation of a national nicotine reduction policy for cigarettes, and such a policy may reduce the reinforcing efficacy of cigarettes and ultimately reduce tobacco dependence. However, it is not yet known how different levels of nicotine may affect the reinforcing efficacy of cigarettes in adolescents. We aimed to determine how reduced nicotine content may affect adolescents' demand for cigarettes using the cigarette purchase task (CPT). **Methods:** Adolescent daily smokers (ages 15-19, N = 50) completed a CPT for their usual brand cigarette and for each dose of SPECTRUM research cigarettes (15.8, 5.2, 1.3, 0.4 mg nicotine/g tobacco) during 4 laboratory sessions. We conducted repeated measures ANOVAs to evaluate the effect of nicotine dose on 5 demand indices derived from the CPT. **Results:** Tests revealed significantly higher demand for usual brand than each research cigarette dose (all p*s* < .01); dose did not significantly affect any measure when usual brand was excluded. **Conclusions:** These results demonstrate the potential utility of the CPT for comparing the reinforcing efficacy of cigarettes varying in nicotine content in adolescents, and indicate a significantly reduced reinforcing efficacy of all research cigarettes relative to usual brand.

Key words: adolescent; smoking; regulatory science; nicotine
***Tob Regul Sci.*™ 2019;5(2):105-114**
DOI: https://doi.org/10.18001/TRS.5.2.2

The passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) gave the United States (US) Food and Drug Administration (FDA) the authority to regulate the manufacture, distribution, and marketing of tobacco products.[1] The FDA has announced its intention to move forward with a plan to reduce the nicotine content in cigarettes to decrease the addictiveness of these products, and eventually, lessen the public health toll of tobacco-related disease.[2] Research studies investigating the potential impact of a mandated nicotine reduction policy on smoking, nicotine dependence and health have been reported, with others currently underway.[3,4] Of particular importance to the FDA is to investigate the implications of this proposed tobacco policy for those most vulnerable to tobacco use. As approximately 90% of cigarette smokers try their first cigarette before age 18, and over 1000 adolescents become cigarette smokers each day, adolescents represent a priority population for the FDA.[5]

Nicotine is the primary constituent in cigarettes responsible for addiction.[6] In 1994 it was proposed that mandating a reduction in nicotine content of cigarettes below a reinforcing threshold that sustains addiction may reduce nicotine dependence and rates of addiction on a population scale.[7] The intent of the policy is to shift behavior away from

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combustible cigarette smoking and toward quitting or to the use of reduced harm products such as nicotine replacement therapies. However, the extent to which cigarette nicotine reduction may reduce the reinforcing efficacy of cigarettes in adolescents is unknown. Like adult smokers, adolescent smokers experience significant negative effects of smoking such as respiratory symptoms and withdrawal symptoms and craving during abstinence.[8-10] However, despite their shorter smoking histories, adolescents tend to be less responsive than adults to empirically-supported cessation interventions.[11] Furthermore, adolescent smoking is highly related to peer influence, marketing, and other non-nicotine factors that may influence cigarette reinforcing efficacy; therefore, adolescents may not respond in the same way to reduced-nicotine content cigarettes as adults.[12,13] Thus, studies assessing the reinforcing efficacy of reduced-nicotine content cigarettes are vital to understanding how adolescents may respond to a mandated nicotine reduction policy to make informed policy decisions. Furthermore, clinical trials using reduced nicotine cigarettes have provided these cigarettes to study participants free of charge; potentially introducing another variable that may influence smoking behavior. As adolescents are sensitive to changes in cigarette cost, it is important to understand how their sensitivity to cost may be affected by nicotine reduction.[14]

The concept of reinforcing efficacy is central to behavioral economics, a theoretical framework which applies consumer demand theory and economic concepts to understanding behavior.[15] A common behavioral economics task used to assess the reinforcing efficacy of cigarettes is the cigarette purchase task (CPT).[16,17] The CPT is a questionnaire assessing cigarette demand in a hypothetical scenario, wherein participants are asked: "How many cigarettes would you smoke in a day if they cost $X?" From the resultant data, a demand curve can be constructed that relates price to consumption. Five demand indices can be derived from the data to provide an indication of how the cigarettes differ in reinforcing efficacy. The CPT has been validated in adolescent smokers with concordance between measures of demand and smoking rate, smoking biomarkers, and nicotine dependence.[18,19] The CPT provides an expedited and cost-efficient method for measuring reinforcing efficacy of reduced and very low nicotine content (~0.4 mg nicotine /g tobacco, VLNC) cigarettes.[20]

A few studies have used the CPT to compare the relationships among nicotine content of cigarettes, cigarette price, and cigarette demand in adults.[21,22] One large multi-site clinical trial randomly assigned adults to receive their usual brand cigarettes or a research cigarette with one of 5 nicotine contents (15.8, 5.2, 2.4, 1.3, or 0.4 mg nicotine/g tobacco).[3,22] Following 6 weeks of exposure to their assigned study cigarette, participants completed the CPT. Responses to the purchase task correlated with actual smoking behavior during the study, and cigarette demand indices derived from the CPT showed that cigarette demand decreased systematically in response to the decreased nicotine content of the cigarettes. The second study, also a large multi-site trial, investigated the acute effects of cigarettes varying in nicotine content among several vulnerable adult populations (smokers with opioid use disorders, affective disorders, and socioeconomically-disadvantaged women).[21] Participants completed the CPT after sampling 4 cigarettes varying in nicotine content (15.8, 5.2, 2.4, and 0.4 mg). Again, demand indices from the CPT varied dose-dependently and indicated a lower reinforcing efficacy for each of the lower-nicotine content cigarettes (5.2, 2.4, and 0.4 mg) relative to the normal nicotine content cigarette (15.8 mg/g) for 3 main indices from the CPT (Intensity, Break point and Maximum Output) described below in further detail.

To our knowledge, only one study has assessed the effect of VLNC cigarettes on withdrawal and subjective response in adolescents, and no studies have yet used the CPT to assess the relative reinforcing effects of reduced nicotine content cigarettes in adolescents. In the primary study from which these data came, adolescent smokers smoked one cigarette of varying nicotine doses after overnight abstinence.[23] Whereas all doses of research cigarettes significantly reduced withdrawal and negative affect, there was not a statistically significant effect across dose for these outcomes; however, there was a statistically significant effect of dose such that higher nicotine content research cigarettes reduced craving and increased positive subjective evaluations to a greater extent than reduced nicotine content cigarettes. These data are generally consistent with findings from adults; however, reinforcing efficacy can provide a more robust measure of abuse

liability than subjective evaluations as it measures demand across a series of increasing prices or constraints.[20] Thus, the current study aimed to test the relative reinforcing efficacy of nicotine in cigarettes following acute exposure in adolescents who had abstained from smoking overnight.

METHODS

Participants

Fifty adolescent (15-19 years old, inclusive) current smokers were recruited from the community and local high schools. Following a phone screen which queried cigarette use, alcohol and drug use, and quit intentions, participants who met initial eligibility criteria were invited to an in-person screening session. For participants under 18, parents were contacted via phone and asked to give verbal consent. Parents were then mailed a paper consent form which they were required to sign, and their child was required to bring with them to the session to participate. Minor participants also gave written assent.

Inclusion Criteria

In addition to self-reporting daily smoking (≥ 28 of the last 30 days) and having been smoking daily for at least the past 6 months, participants had to submit a breath carbon monoxide (CO) sample measured using a Smokerlyzer ED50 meter (Bedfont Instruments) of > 6 ppm at their screening session. If they did not, they were required to submit a urine sample, which was tested for cotinine using NicAlert strips. A test result of 3 or higher (approximately equivalent to a Cotinine Concentration of 100-200 ng/mL) was required to verify smoking status. In addition, participants could not be suicidal, pregnant or breastfeeding, using alcohol or other drugs daily (except marijuana), or planning to quit smoking for good within the next month.

Experimental Procedures

At the baseline session, adolescents were screened in person for eligibility and also completed baseline measures. Following this session, if eligible, adolescents were given instructions about their next 4 sessions. They were instructed to abstain from smoking starting at 10 pm the night before their scheduled session and informed that their breath CO would be tested to determine any recent smoking. CO values had to be ≤6 ppm or a 50% decrease from their baseline CO measure, whichever was higher. Adolescents also were asked to sign an affidavit stating that they had not used tobacco since the night before. During the session, adolescents smoked a single research cigarette in the laboratory using a CReSS pocket device (CReSS Pocket, Borgwaldt KC, Richmond VA). Shortly after smoking the cigarette, adolescents answered questions about the cigarette they had just smoked. Doses of research cigarettes were presented in counterbalanced order across participants, and both participant and researchers were blind to the dose presented. Participants were paid $25 at screening, regardless of eligibility, and $35 for each experimental session completed; completing all 4 sessions resulted in a $100 bonus payment to incentivize study completion.

Products Tested

SPECTRUM brand research cigarettes were provided by the National Institute on Drug Abuse and produced by 22nd Century Group, Inc. The 4 doses tested in the current study had 15.8, 5.2, 1.3 and 0.4 mg/g of tobacco, and all tar yields were 9 ± 1.5 mg. 15.8 mg/g is approximately equivalent to nicotine content in a commercial cigarette. Although not tested in the current study, we also collected data on participants' usual brand cigarettes. These cigarettes, based on available FTC data, are generally above or in the range of the normal nicotine content cigarettes (15.8 mg/g condition).

Measures

Modified Fagerström Tolerance Questionnaire (mFTQ). Adapted from the Fagerström Tolerance Questionnaire, this is a measure of nicotine dependence and has been validated for use in adolescents.[24,25]

Cigarette purchase task (CPT) - usual brand. In this questionnaire, adolescents were asked to imagine that the available cigarettes were their usual brand and they had no access to other sources of their usual brand cigarettes, and they were not to save or stockpile cigarettes for later. Given these instructions, they were to report how many of their usual brand cigarettes they would purchase in a 24-hour period at a series of increasing prices ($0.00,

Table 1
Correlations between Baseline Variables and Usual Brand Demand Indices Derived from the CPT (N = 50)

	1	2	3	4	5	6	7	8
1. Sex	1	0	-.08	.13	.89	.03	.11	-.04
2. Age		1	-.18	-.03	-.17	-.20	-.11	.11
3. Baseline Dependence (mFTQ score)			1	**.39****	**.28****	.12	**.40****	**-.50****
4. Intensity (Usual Brand)				1	**.40****	.17	**.47****	**-.49****
5 Break Point (Usual Brand)					1	**.81****	**.57****	**-.54****
6. Pmax (Usual Brand)						1	**.67****	**-.41****
7. Omax (Usual Brand)							1	**-.50****
8. Alpha (Usual Brand)								1

Note.
Asterisks denote a significant correlation (p < .01).

$0.02, $0.05, $0.10, $0.20, $0.30, $0.40, $0.50, $0.60, $0.70, $0.80, $0.90, $1.00, $2.00, $3.00, $4.00, $5.00). This task has been validated for use in adolescents.[17,19] This CPT was administered at baseline.

Cigarette purchase task (CPT) - study cigarettes. The questionnaire was identical to the cigarette purchase task - usual brand, with the exception that in the instructional set participants were asked to imagine that the available cigarettes were their "study cigarette from today."[22] These CPTs were administered in each study session immediately after smoking the research cigarette.

Data Analysis

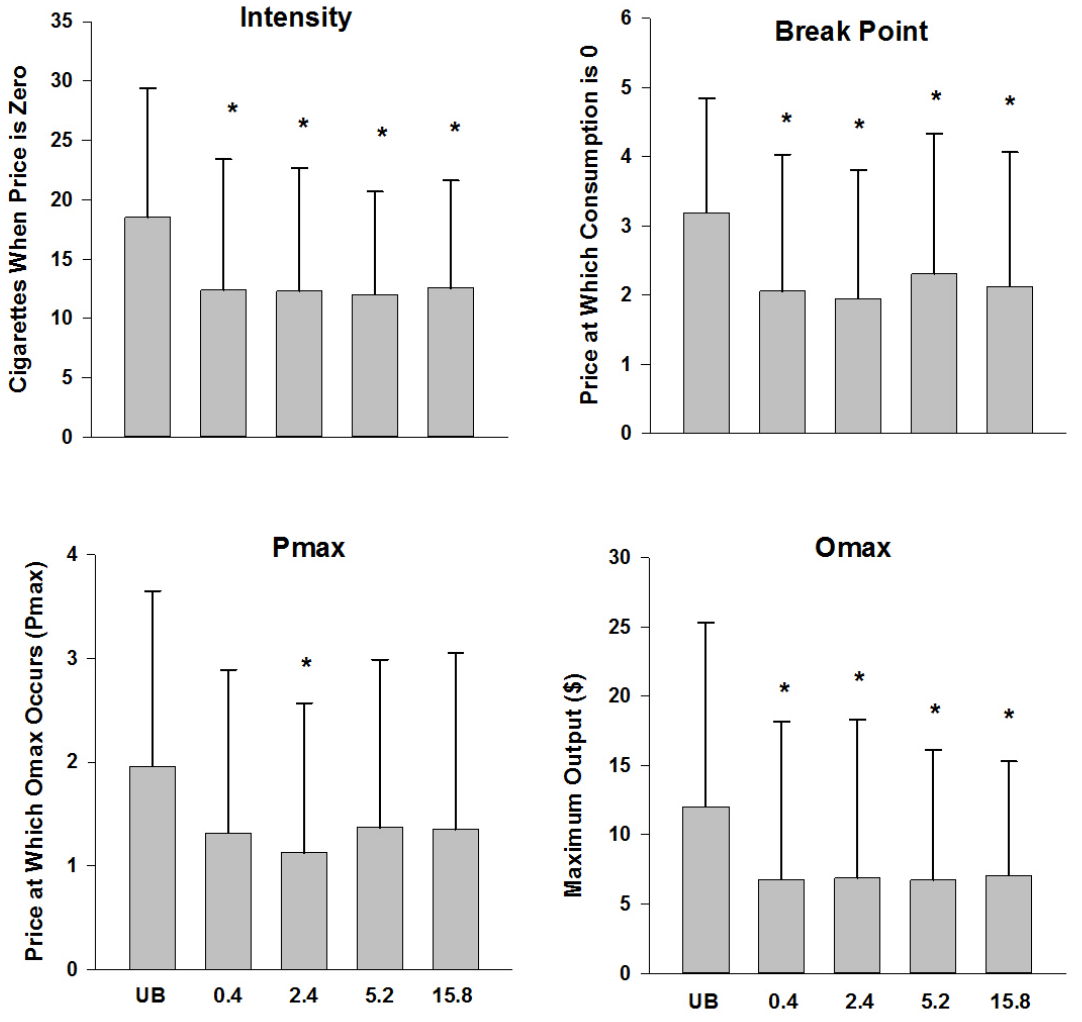
Cigarette purchase task demand indices. Several demand indices can be derived from the data that reflect multiple dimensions of the relative reinforcing efficacy of the drug to the individual across changes in response cost: *Intensity*, or the amount of cigarettes participants report they would consume when they are free; *Breakpoint*, the first price at which demand was suppressed to zero; *Omax*, the maximum amount that participants would spend on cigarettes across all prices; *Pmax*, the price at which Omax is reported and α, a measure of the 'sensitivity of behavior to changes in price,' which is derived from the following equation:[26]

$$Y = Q_0 * 10^{k(e^{-\alpha Q_0 C} - 1)}$$

where Q represents cigarettes consumed and C is cigarette price, k is set to a constant of 3 in the current analyses), and Q_0 is the estimate of cigarette consumption at zero price. The rate parameter α represents the rate of change in elasticity of demand across the demand function and is inversely related to reinforcing efficacy, such that lower α values indicate greater reinforcing efficacy.[27] Thus, in the current analyses, all indices were derived empirically from observed data with the exception of α.

Prior to implementing statistical procedures, purchase task data were examined for orderliness according to the methods laid out by Stein et al.[28] One participant's data in dose 2 met criteria for an intensity value greater than 3 standard deviations above the mean; this value was recoded to 3 standard deviations above the mean. No data were excluded for inconsistent responding. Several participants' data were excluded from analyses using the exponentiated demand equation due to null demand; these data are explained further under the null demand section). For participants who did not suppress their responding to zero (ie, did not reach breakpoint), the breakpoint value was recoded as the highest tested price ($5).

Figure 1
Mean And Standard Deviation of Intensity, Breakpoint, Omax, and Pmax across Dose



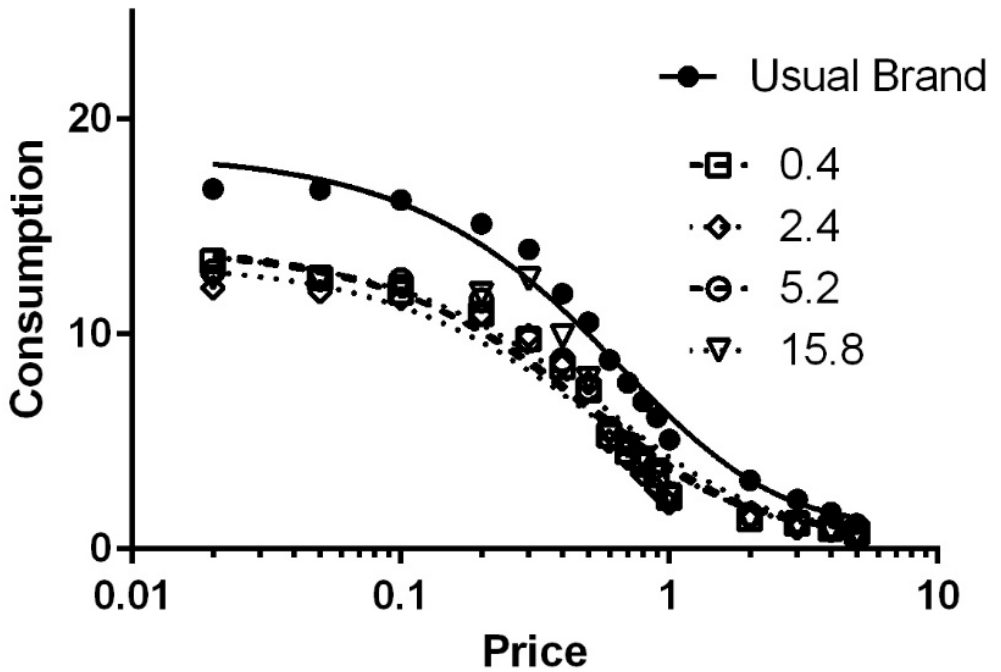
Note.
Asterisks denote a significant difference relative to usual brand.

Correlations. We examined correlations between demand indices and participant characteristics to determine if relationships existed between reinforcing efficacy of usual brand cigarettes and sex, age, and cigarette dependence in this sample.

Dose effects on intensity, breakpoint, Omax and Pmax. The effects of nicotine dose were examined using repeated measures ANOVAs in SPSS version 24 for Windows (IBM). We tested models including all 4 doses of research cigarettes and usual brand, as well as all 4 research doses without usual brand to determine the effects of nicotine dose relative to usual brand and to determine any effects across dose within research cigarettes.

Comparison of α values across dose. The α values for each average curve at each dose were compared using an extra sum-of-squares F-test (Prism version 6 for Windows, GraphPad Software, San Diego CA). This procedure tests the null hypothesis that one α parameter best fits the data; rejecting the null hypothesis indicates that the α parameter is not shared across data sets, indicating significant-

Figure 2
Mean Fitted Curves of Demand for Cigarettes across Dose



ly different α values across dose.

Null demand analysis. Several of the participants noted that they would not purchase any study cigarettes, even if they were free. Although their data were included in the empirically derived parameters, fitted demand curves could be not be derived from these individuals' data, and therefore, they are not reflected in the α value analysis. However, a lack of demand for these cigarettes is an important facet of abuse liability that we wished to capture. Thus, we expressed these data as the number (count) of participants who expressed null demand at price zero as a function of nicotine dose.

RESULTS

Participant Characteristics

The average age of the participants was 17.7 (SD = 1.0), and 56% were menthol smokers. There were equal numbers of females and males. Of the participants, 47.2% were white, 19.4% were black, 13.9% were Asian, and 14% reported Hispanic ethnicity. Participants smoked an average of 8.2 (SD = 4.5) cigarettes per day and their average CO at baseline was 11.2 ppm (SD = 7.2). The average dependence score was 4.2 (SD = 1.5) indicating moderate dependence.

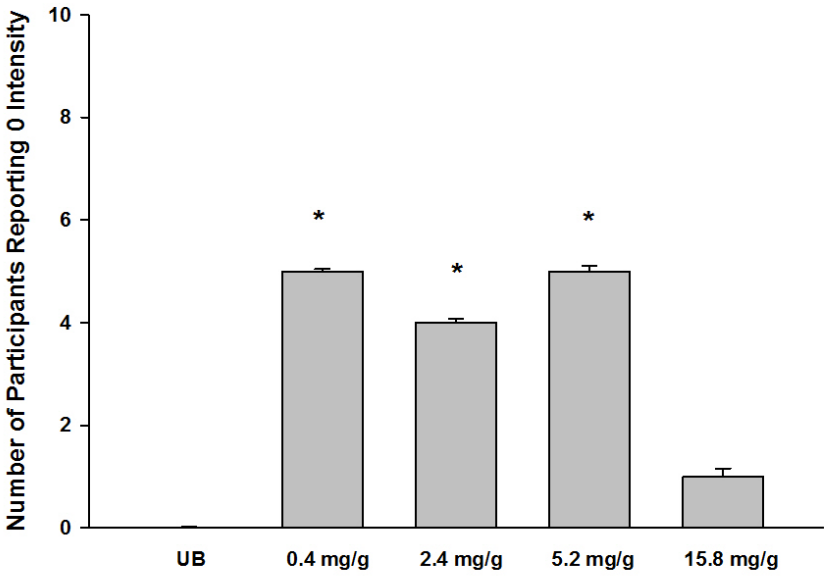
Correlations

Table 1 shows the bivariate correlations. All demand indices with the exception of Pmax were significantly and positively associated with dependence. No outcomes were significantly associated with age or sex. All demand indices were also significantly correlated with each other, with the exception of Pmax and intensity.

Dose Effects on Intensity, Breakpoint, Omax, and Pmax

Figure 1 shows the raw values for Intensity, Breakpoint, Omax, and Pmax across dose. All demand indices (Intensity, Breakpoint, Omax, Pmax) were checked for normality; the distribution for Omax was non-normal and logarithmically transformed prior to running ANOVAs. All other variables were

Figure 3
Percent of Participants Reporting that They Would Smoke Zero Cigarettes if They Were Free at Each Dose



Note.
Asterisks denote a significant difference relative to usual brand.

normal. When entering 5 doses (usual brand and 4 research cigarette doses), there was a main effect of cigarette type on intensity ($F(2.915, 142.813) = 9.62$, $p < .001$; Greenhouse-Geisser correction); Breakpoint ($F(2.694, 131.999) = 11.743$, $p < .001$; Greenhouse-Geisser correction), log Omax ($F(2.928, 143.489) = 6.209$, $p < .001$; Greenhouse-Geisser correction); and Pmax ($F(3.03, 148.489) = 4.801$, $p < .003$; Greenhouse-Geisser correction). For Intensity, Breakpoint, and Omax, *post hoc* comparisons indicated that usual brand was significantly different from all Spectrum doses (all p*s* < .10), whereas no Spectrum doses were significantly different from one another. For Pmax, the only statistically significant *post hoc* comparison was usual brand versus the 2.4 mg/g Spectrum dose. When usual brand was excluded from the analyses, dose was not statistically significant for any outcome.

Comparison of α Values across Dose

The global fits of Equation 1 to the data from each dose are shown in Figure 2. The average R^2 values were greater than 0.85 across all doses (Usual brand, M = .88; 0.4 mg dose, M = .87; 1.2 mg dose, M = .88; 5.2 mg dose, M = .89; 15.8 mg, M = .86), indicating very good fit to the data. An extra sum-of-squares F Test indicated that α was not shared across cigarette type ($F(4,4002) = 11.90$, $p < .001$). In other words, consistent with the data from the other demand indices, one α value did not describe the data when including the usual brand condition.

Null Demand Analysis

Figure 3 shows the count of participants who expressed zero demand for their usual brand cigarettes when they were free. A nonparametric test, the related-samples Cochran's Q test, indicated that after re-coding the data sets for 'zero' or non-zero the distributions for the 5 doses tested were significantly different from each other ($p = .016$). Specifically, the distribution of participants who reported that they would not "buy" any study ciga-

rettes if they were free of charge was significantly higher in the 0.4 - 5.2 mg/g Spectrum conditions (4-5 participants) relative to the usual brand condition (0 participants), and was significantly greater for the 0.4 mg/g and 5.2 mg/g dose relative to the 15.8 mg/g dose.

DISCUSSION

As a nicotine reduction policy gains momentum, understanding how such a policy would reduce the reinforcing efficacy of cigarettes in vulnerable populations is an important goal. Furthermore, understanding how cigarette price may interact with cigarette nicotine reduction to affect smoking in adolescents is essential. To that end, we conducted what we believe to be the first laboratory examination of the effect of various nicotine doses on cigarette demand in adolescent smokers. This analysis complements and extends our previous report on the effects of reduced-nicotine cigarettes on cigarette craving, withdrawal symptoms, negative affect, and cigarette evaluations in this sample.[23] Our analysis showed that relative to usual brand, the reinforcing efficacy of all doses of research cigarettes was reduced; however, when compared to each other, no dose of research cigarettes differed significantly from each other. We did find that participants were more likely to report null demand (ie, reported that they would not consume any cigarettes at any price) at the 0.4, 2.4, and 5.2 mg/g reduced nicotine doses, but not at the 15.8 mg/g research cigarette dose. The null demand results comport with data from the same study, which demonstrated that participants showed decreased subjective satisfaction from the research cigarettes as a function of dose.[23] Intuitively, the lack of demand for any cigarettes, even when they are free, suggests that the null demand analysis may track more closely to subjective evaluation or 'disliking'.

The current data differ from similar studies with adults. In contrast to the current data which did not show a significant difference across doses, Higgins et al[21] found a graded effect of nicotine dose on indices from the CPT in a similar acute model of exposure in adults. However, as noted above, in this same sample of adolescents we found a graded effect of dose on craving reduction and subjective responses.[23] This suggests that dose did influence some responses and underscores the idea that participants were able to discriminate nicotine dose. It is interesting to note that although our study did not show a dose-response effect, adolescent smokers had lower levels of demand for the SPECTRUM research cigarettes overall. For example, in adults, the reported intensity for the 15.8 mg/g cigarettes was around 18 cigarettes, whereas for adolescent participants, it was 12.5 cigarettes. In contrast, intensity for usual brand cigarettes was similar to what is seen in adult smokers of similar cigarettes per day (eg, around 19 cigarettes),[29] suggesting that adolescents may be particularly sensitive to branding as all research cigarettes were of an unfamiliar brand regardless of dose. Similarly, whereas adults in the Higgins et al[21] trial described above gave 15.8 mg/g cigarette a smoking satisfaction score of 4.6 on a 1-5 scale, and VLNC cigarettes a 3.2, on average; adolescents in the current study reported an average smoking satisfaction score of just 3.2 for the 15.8 mg/g cigarette, and an average of 2.5 for the VLNC cigarette.[23] These results suggest that adolescents are relatively less subjectively satisfied by, and in turn, do not show as strong demand for, research cigarettes when compared to adults.

Although the extent to which these results may change after longer-term exposure is currently not known, some insights can be gleaned from data from a large trial in which adults were exposed to 6 weeks of research cigarettes at different doses. In that study, young adults (ages 18-24) in the VLNC group (0.4 mg nicotine/g tobacco) showed less subjective reinforcement from these research cigarettes relative to older smokers (ages 25+) after 2 weeks of use.[30] Emerging from these results is an overall picture that points to reduced reinforcing efficacy for research cigarettes in younger smokers relative to older adults, which suggests that young people may be even more sensitive to the effects of nicotine reduction on cigarette reinforcement than older smokers. However, an important caveat remains that these data are all based on studies using an unfamiliar brand of research cigarettes; given the apparent sensitivity to brand-switching in this population, it is difficult to determine if these results would be same with low nicotine cigarettes that retained the branding elements of participants' usual brand cigarettes. In the current study, participants were exposed to each cigarette dose once in a blinded presentation. This may account for the lack of dose-response signal among the main de-

mand indices, although such exposure did result in greater null demand at lower doses.

This study must be understood in the context of several limitations. The first is that whereas it provides important information regarding the acute response to these cigarettes, it is not possible in the context of this study to determine how changes in reinforcing efficacy may impact quitting or switching to new products. In adults, Smith et al[22] found that not only was the reinforcing efficacy of VLNC cigarettes lower relative to higher dose cigarettes, extended exposure to VLNC cigarettes also reduced participants' demand for their usual brand of cigarettes, indicating a potential mechanism by which such a policy may facilitate eventual abstinence from cigarettes. Second, due to ethical constraints related to administering cigarettes in the lab, our study population included only adolescent daily smokers. Many adolescents are nondaily smokers, and thus, our study may not generalize to these youth.[31] At the same time, young daily smokers are at the highest risk of continuing to smoke as adults, and therefore, comprise a population of interest for regulatory effort, and these data also provide an important direct comparison with adult daily smokers. Third, participants completed the CPT for study cigarettes after only a single, blinded exposure following overnight abstinence. The usual brand CPT analyzed here was administered at baseline when participants were not in withdrawal. However, at each session following the study CPT administration, participants also were administered their usual brand CPT; the indices from the session CPTs did not differ from baseline, mitigating this concern. Finally, although well-validated with real-world behavior, the CPT is a self-report measure of reinforcing efficacy, and it is likely that a behavioral choice task would delineate different aspects of dose differences in reinforcing efficacy. Future research should triangulate these results with behavioral self-administration tasks in adolescent tobacco users.

IMPLICATIONS FOR TOBACCO REGULATION

These results demonstrate the potential utility of the CPT for comparing the reinforcing efficacy of cigarettes varying in nicotine content in adolescents, and indicate a significantly reduced reinforcing efficacy of all research cigarettes relative to usual brand. This study, along with others, suggests that nicotine reduction would be an effective approach to reducing smoking reinforcement in adolescent daily smokers. As a comprehensive nicotine reduction plan moves forward, it is important to continue to model the potential effects of this policy on adolescents and young adults. Indeed, some models have suggested that if the FDA enacts the policy by 2020, then by 2060 there will be a cumulative reduction in new smokers of ~16 million.[32] Such a policy has the potential to transform the future health of young people by reducing reinforcement from combustible cigarette use, and to reduce the public health toll of combustible cigarette use.

Human Subjects Approval Statement

All procedures were approved by the Brown University Institutional Review Board.

Conflict of Interest Disclosure Statement

The authors have no conflicts of interest to report.

Acknowledgements

The study was funded by NCI grant 1K01CA189300 (RNC). Support for the preparation of this paper was also provided by NIDA grants U54DA031659 (JWT, RD-A and SMC) and P50DA036114 (JWT). Research reported in this publication was supported by NCI and FDA Center for Tobacco Products (CTP). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. Research cigarettes were supplied by NIDA.

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